Ischaemic stroke in incident dialysis patients

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Abstract

Background. Despite the high frequency of cardiovascular disease among the population on dialysis, there are few studies on ischaemic stroke and associated factors. The objective of the present study is to assess the prevalence of ischaemic stroke at the start of dialysis, its incidence in the course of follow-up and possible factors associated in its presentation.

Methods. All patients in our dialysis programme between 1 January 1999 and 31 December 2005 were included in the study and followed up until death, transplant, transfer out of our catchment area, or conclusion of the study on 31 December 2008. Factors analysed were age, gender, smoking habit, diabetes, hypertension, previous ischaemic stroke, ischaemic coronary disease, peripheral vascular disease and atrial fibrillation. Other factors measured in the first month of dialysis were haematocrit, urea, creatinine, lipids, calcium, phosphorus, parathyroid hormone and albumin.

Results. Of 449 patients included in the study (age 64.4 ± 16 years), 30 commenced dialysis having had previous stroke (prevalence 6.7%). In a follow-up of 38.77 ± 29 months, 34 patients presented with one or more strokes; an incidence of 2.41/100 patient-years. Greater age [odds ratio (OR): 1.05; 95% confidence interval (CI): 1.01–1.09; P = 0.007], diabetes (OR: 2.29; 95% CI: 1.15–4.55; P = 0.018) and presence of atrial fibrillation (OR: 3.11; 95% CI: 1.53–6.32; P = 0.002) were independent predictors of stroke occurrence.

Conclusions. The prevalence of ischaemic stroke is high at the commencement of dialysis, and its incidence is elevated in the course of follow-up. As with the general population, atrial fibrillation is an important factor predictive of ischaemic stroke, and as such, the clinical implication is that prophylactic anti-coagulation therapy needs to be considered for these individuals.

Keywords: atrial fibrillation; dialysis; ischaemic stroke; mineral metabolism

Introduction

Atherosclerotic cardiovascular disease is known to be the principal cause of death in patients on dialysis. Despite atherosclerosis being a systemic disease, attention has centred mainly on some cardiac aspects/manifestations such as left ventricular hypertrophy or ischaemic heart disease. The few studies available on cerebrovascular disease date from the decade of the 1990s in the Japanese dialysis population in which a higher incidence of haemorrhagic was observed compared to ischaemic stroke [1].

More recently, evidence has been presented showing changes in the distribution of cardiovascular events in patients on dialysis, i.e. a higher presence of cerebrovascular disease in the form of ischaemic stroke [2–4]. It is possible that these changes result from the patients currently accessing dialysis being older and with a higher co-morbidity.

Until quite recently, other risk factors that may be present in patients on dialysis had not been identified, including the presence of atrial fibrillation (AF) in any of its clinical patterns of presentation [5], which could be contributing to the cerebrovascular disease in the population on dialysis.

The objective of the present study is to analyse the prevalence of ischaemic stroke in patients accessing the dialysis programme, the incidence of stroke in the clinical follow-up and the factors related with its presentation.

Materials and methods

We included patients with end-stage renal disease (ESRD) who commenced dialysis (haemodialysis or peritoneal dialysis) between 1 January 1999 and 31 December 2005 in our health provision catchment area (one dialysis unit in the central hospital and two peripheral clinical centres). Excluded were those patients who had commenced treatment in another centre, who had received a transplant or who had a recovered renal function.

The period of observation was from the first day on dialysis up to the day of transfer for transplant, death, transfer of the patient out of our catchment area or the close of study on 31 December 2008.

We analysed the prevalence of ischaemic stroke prior to the commencement of dialysis, its appearance in the clinical monitoring during dialysis and the factors related with its presentation. Not included were the episodes of transient ischaemic attack (TIA) or lacunar infarcts. The following variables were analysed: demographic data, diagnosis of diabetes at the start of dialysis, hypertension, smoking habit, documented coronary disease, advanced peripheral artery disease, atrial fibrillation and dialysis modality in follow-up (peritoneal or haemodialysis). In the first month of dialysis, the haematocrit, urea, creatinine, total cholesterol, triglycerides, calcium, phosphorus, intact parathyroid hormone (iPTH) and albumin were measured. The electrocardiogram (ECG) was performed on entry into the dialysis programme, annually thereafter and when the clinical circumstances necessitated it.
Definitions

Ischaemic stroke: Having focal neurological deficit persisting for >24 h (excluding haemorrhage) using computed tomography or magnetic resonance imaging, according to the opinion of the attending neurologist.

Documented coronary disease: Having an acute myocardial infarction or having had a coronary angiography showing >70% stenosis in the epicardiac arteries.

Advanced peripheral artery disease: Having disease of the arteries of the lower limbs in La Fontaine stage IV, or critical ischaemia and/or amputation of lower limbs for reasons other than trauma, neoplasia or vasculitic disease.

Atrial fibrillation: AF was considered when the arrhythmia was present in the initial evaluation for dialysis, or when there was a previous ECG documenting the condition. An episode of AF was considered in the clinical evolution/follow-up if documented by ECG.

Diabetes: Diagnosis of diabetes with indication of pharmacological treatment at any time in the course of the clinical follow-up.

Arterial hypertension: Patients with indication of hypotensive medication prescribed to reduce arterial pressure to <140/90 mmHg.

Smoking habit: Active smoker at the start of the dialysis or having stopped smoking <10 years previously.

Statistical analyses

Comparison of means was with the Student’s t-test or the non-parametric Mann–Whitney test. The Pearson χ² test was used for the comparison of qualitative variables. Multivariate analysis was performed using logistic regression to establish the association of prior ischaemic stroke with factors measured at the start of the dialysis programme. The prognostic variable was the appearance of ischaemic stroke in follow-up. The study was based on an analysis of the predictors at the start of the treatment using the Cox’s proportional risk regression. All the measured variables were included in the analyses. The best predictive model was obtained using the procedure of conditional progressive incorporation. The odds ratios and the 95% confidence intervals were calculated. Survival analysis was performed using the Kaplan–Meier method, and the comparison of survival curves was with the Mantel–Haenszel log-rank test. A P-value of <0.05 was considered statistically significant. The analyses were performed with the SPSS package (version 11.0) for Windows.

Results

Patients included in the study

There were 531 patients on dialysis, of which 82 (15.4%) were excluded from the study because of having had an earlier transplant (n = 37; 6.9%), having begun dialysis in a different centre (n = 21; 3.9%), having had a recovered renal function (n = 14; 2.6%), having had died before the ESRD diagnosis was established (n = 5; 0.9%) and having left our catchment area (n = 5; 0.9%). The remaining 449 patients form the current study sample.

The origins of the ESRD nephropathy were glomerulonephritis (16.5%), interstitial nephropathy (14.3%), diabetes (14.9%), nephroangiosclerosis (12.9%), systemic disease (9.1%), polycystic kidney disease (6.5%), familial nephropathy (2.2%), unknown (21.4%) and others (2.2%). Of the overall patient group, 375 (81.3%) were on haemodialysis, and 84 (18.7%) were on peritoneal dialysis.

The mean follow-up was 38.77 ± 29 months, representing an observation period of 1450 patient-years.

Prevalence of ischaemic stroke on commencing dialysis

There were 30 patients who had had one or more ischaemic strokes before beginning dialysis. This represents a prevalence of 6.7% of patients who began dialysis with a diagnosis of ischaemic stroke.

Table 1 summarizes the characteristics of the patients who had presented with one or more ischaemic strokes before commencing dialysis. In the multivariate analysis, greater age, more ischaemic heart disease, AF and lower levels of plasma calcium were associated with the diagnosis of previous ischaemic stroke (Table 2).

Incidence of patients with ischaemic stroke on follow-up

Over the period of dialysis, 34 (7.5%) patients suffered one or more ischaemic strokes; 7.7% of the males and 7.3% of the women (n = 19 males and n = 15 females, respectively). The incidence was 2.41/100 patient-years of follow-up.

In the follow-up, 79 patients were diagnosed de novo as having AF in any of its manifestations (permanent or non-permanent); 49 of the 112 patients (43.7%) with AF (at the start or during follow-up) received treatment with coumarine derivatives.

Table 1. Characteristics of the patients with stroke prior to entry into the dialysis programme

<table>
<thead>
<tr>
<th>Variable</th>
<th>All n = 449</th>
<th>No ischaemic stroke n = 419</th>
<th>With ischaemic stroke n = 30</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>64.4 ± 15</td>
<td>63.9 ± 16</td>
<td>71.7 ± 9.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Males</td>
<td>245 (54.6%)</td>
<td>225 (53.7%)</td>
<td>20 (66.7%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>391 (87.1%)</td>
<td>362 (86.4%)</td>
<td>29 (96.7%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>104 (23.2%)</td>
<td>94 (22.4%)</td>
<td>10 (33.3%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>170 (9.3%)</td>
<td>155 (37.2%)</td>
<td>15 (50%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Documented coronary disease</td>
<td>29 (6.5%)</td>
<td>22 (5.3%)</td>
<td>7 (23.3%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Advanced peripheral vascular disease</td>
<td>28 (6.2%)</td>
<td>23 (5.5%)</td>
<td>5 (16.7%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Previous atrial fibrillation</td>
<td>33 (7.3%)</td>
<td>26 (6.2%)</td>
<td>7 (23.3%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Haematocrit; %</td>
<td>32.3 ± 5.2</td>
<td>32.2 ± 5.2</td>
<td>33.2 ± 5.8</td>
<td>0.31</td>
</tr>
<tr>
<td>Urea; mg/dL</td>
<td>147.2 ± 51</td>
<td>147.6 ± 51</td>
<td>142.2 ± 45</td>
<td>0.56</td>
</tr>
<tr>
<td>Creatinine; mg/dL</td>
<td>7.42 ± 2.6</td>
<td>7.49 ± 2.6</td>
<td>6.56 ± 1.8</td>
<td>0.059</td>
</tr>
<tr>
<td>Calcium corrected for albumin; mg/dL</td>
<td>9.2 ± 1.1</td>
<td>9.57 ± 1</td>
<td>9.04 ± 1</td>
<td>0.007</td>
</tr>
<tr>
<td>Phosphorus; mg/dL</td>
<td>5.28 ± 1.9</td>
<td>5.31 ± 1.9</td>
<td>4.91 ± 1.4</td>
<td>0.4</td>
</tr>
<tr>
<td>iPTH; pmol/mL</td>
<td>220.4 ± 249.5</td>
<td>218.5 ± 251.6</td>
<td>246.4 ± 219.8</td>
<td>0.55</td>
</tr>
<tr>
<td>Albumin; g/dL</td>
<td>3.62 ± 0.56</td>
<td>3.62 ± 0.55</td>
<td>3.65 ± 0.59</td>
<td>0.75</td>
</tr>
<tr>
<td>Cholesterol; mg/dL</td>
<td>170 ± 48</td>
<td>170.3 ± 48</td>
<td>165.7 ± 52</td>
<td>0.61</td>
</tr>
<tr>
<td>Triglycerides; mg/dL</td>
<td>158 ± 89</td>
<td>159.8 ± 90</td>
<td>134.6 ± 69</td>
<td>0.068</td>
</tr>
</tbody>
</table>
The patients who presented with stroke in the follow-up were older. There were a higher proportion of patients with diabetes and AF diagnosed at any time during follow-up. Of these 34 patients, six (17.6%) had presented with ischaemic ictus before commencing dialysis (Table 3). In the multivariate analysis, the predictive factors for ischaemic stroke were higher age, diagnosis of diabetes and AF (Table 4). Of the 34 patients who presented with stroke, 20 had AF; an incidence of 5.83/100 patient-years compared to the incidence of ischaemic stroke of 1.31/100 patient-years in those who were in sinus rhythm. Only two of the 34 patients who had ischaemic stroke in follow-up were on treatment with coumarin derivatives, one of them with an international normalized ratio (INR) below the therapeutic value at the time of the event.

Of the 34 patients, 28 had had the first stroke subsequent to entry into the dialysis programme. The incidence was 2.08/100 patient-years. The factors predictive of de novo stroke were greater age (OR: 1.042; 95% CI: 1.004–1.085; P = 0.030), AF diagnosed at any time during the clinical follow-up (OR: 2.94; 95% CI: 1.41–6.12; P = 0.004), diagnosis of diabetes (OR: 2.16; 95% CI: 1.05–4.43; P = 0.035), higher calcium concentrations (OR: 1.31; 95% CI: 1.01–1.70; P = 0.03) and lower albumin concentrations (OR: 0.31; 95% CI: 0.14–0.66; P = 0.003).

Mortality and ischaemic stroke

Of the 30 patients who commenced dialysis with stroke, 24 died in the course of follow-up. At 1 year of dialysis, the survival was 82% in the patients without previous ictus versus 60% in those who had had stroke. At 2 years of follow-up, these values were 72% vs. 39% and, at 5 years, were 47% vs. 24% (Figure 1).

Post-event survival was 15.37 ± 18 months (median = 7.4). There were 28 deaths among these 34 patients; 12 of the deaths were a direct result of the stroke, and five patients abandoned dialysis or died in cachexic state. The other causes of death were cardiovascular (n = 5), sepsis (n = 2), neoplasias (n = 2) and digestive tract bleeding (n = 2).

Discussion

The present study indicates a high prevalence of ischaemic stroke in patients with ESRD at the start of dialysis, as well as a high incidence of ischaemic stroke in the course of a substitutive treatment.

Despite the known high prevalence of cardiovascular disease in the dialysis population, cerebrovascular disease and its manifestation of ischaemic stroke have been poorly studied. Evaluations of stroke prevalence at the start of dialysis are few. The CHOICE study [6] showed rates of stroke of 11%. However, the greater proportion of patients with diabetes and heart disease makes it difficult to compare the results directly with our study. A further difference that makes comparisons difficult is that, in the CHOICE study, enrolment occurred a median of 45 days after the first dialysis, while in the present study, all the patients were included from the first day on the dialysis programme. The DOPPS study showed a stroke prevalence of the deaths were a direct result of the stroke, and five patients abandoned dialysis or died in cachexic state. The other causes of death were cardiovascular (n = 5), sepsis (n = 2), neoplasias (n = 2) and digestive tract bleeding (n = 2).

Discussion

Table 2. Factors associated with ischaemic stroke prior to entry into the dialysis programme (multivariate analyses)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03</td>
<td>(1.00–1.07)</td>
<td>0.048</td>
</tr>
<tr>
<td>Documented CD</td>
<td>4.09</td>
<td>(1.43–11.66)</td>
<td>0.008</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4.06</td>
<td>(1.50–10.98)</td>
<td>0.006</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.60</td>
<td>(0.40–0.90)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

CD, coronary disease.

Table 3. Characteristics of the patients who suffered a stroke in the course of follow-up

<table>
<thead>
<tr>
<th></th>
<th>No ischaemic stroke (n = 415)</th>
<th>Ischaemic stroke (n = 34)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>63.7 ± 15.8</td>
<td>73.6 ± 11.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>89 (21.4%)</td>
<td>15 (44.1%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Previous ischaemic stroke</td>
<td>24 (5.8%)</td>
<td>6 (17.6%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Atrial fibrillation*</td>
<td>92 (22.2%)</td>
<td>20 (58.8%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Calcium; mg/dL</td>
<td>9.49 ± 1.02</td>
<td>10.04 ± 1.2</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Atrial fibrillation diagnosed before entry into the dialysis programme or during follow-up.

Table 4. Factors predictive of ischaemic stroke in follow-up (multivariate analysis)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05</td>
<td>(1.01–1.09)</td>
<td>0.007</td>
</tr>
<tr>
<td>Atrial fibrillation*</td>
<td>3.11</td>
<td>(1.53–6.32)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.29</td>
<td>(1.15–4.55)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

*Atrial fibrillation diagnosed before entry into the dialysis programme or during follow-up.
of 18%, with a variation of 12.5%, 13.7% and 18.5%, depending on ethnicity and geographic area (Japan, Europe and USA, respectively) [7]. The HEMO study showed a prevalence of 19.5% of patients, despite patients with TIA having been included [8].

The few analyses of incidence of ictus in patients on dialysis derive from the Japanese population in the decade of the 1990s. There was evidence of a higher incidence of haemorrhagic ictus compared to ischaemic (0.37/100 and 0.22/100 patient-years, respectively) which was similar to the rate in the general Japanese population [1,9]. The greater incidence of ischaemic stroke in the patient population in the present study can be explained on the basis of the Japanese population on dialysis being 10 and 15 years younger. Also, the proportion of diabetic individuals was lower, which reflects the lower prevalence of diabetes and co-morbidities in the dialysis population in Japan [10]. Recently, there has been evidence of an increase in ischaemic ictus in Japan. The proposed explanation is that dialysis is now being accessed by more elderly patients who have more co-morbidities, together with the ‘westernization’ of the Japanese population [11].

Data from the USRDS registry showed an incidence of 4.79 hospitalizations/100 patient-years in patients on dialysis; 6- to 10-fold greater than in the general population [2]. Other analyses have shown rates of hospitalization for stroke, or fatal stroke without hospitalization, for de novo ictus, of 3.3/100 patient-years. However, these patients were 10 years younger than those of the present study, and half of them had been on dialysis for 2 years [12]. These differences make the comparisons difficult. The CHOICE study encountered an incidence of stroke of 4.9/100 patient-years, with 15.8% of the patients presenting one or more events in a follow-up period of 2.7 years, the majority of the events (76%) being ischaemic [3]. The 4D study [13] analysed the presentation of cardiovascular and stroke events in patients on haemodialysis treated with atorvastatin. All the patients were diabetic and, hence, not suitable for comparison with the present study. More recently, the AURORA study [14] analysed the occurrence of stroke and cardiac events in patients on haemodialysis treated with rosuvastatin. The study was with patients with a mean period on dialysis of 3.5 years. The presentation of events in the overall study population was less than expected. According to the authors, this could be attributable to those patients who were already receiving statins (30–40%), possibly with risk factors or with previous events. This complicates the evaluation of the true incidence of stroke in patients on dialysis and to make comparisons with the present study.

Although the incidence of stroke in the present study is lower than other studies of patients on dialysis, it is greater than that presented by the general population in our environment whose incidence in the 65–74-year age band is 0.284/100 person-years [15]. This implies an incidence of stroke in the patients on dialysis that is 8-fold higher than that of the general population.

The factors related to stroke prior to entry into the dialysis programme were greater age and the more documented coronary disease. These results are concordant with the HEMO study, although our patients with stroke were 7 years older and with a lower proportion of coronary disease [8]. The diagnosis of AF was associated with having had a stroke prior to dialysis. Patients with previous stroke had lower levels of calcium, although this was within the limits set in clinical guidelines in current use. Higher calcium concentration was predictive of de novo stroke. There is a paucity of data on associations between disorders of calcium–phosphorus metabolism and the presentation of adverse cardiovascular events in patients with chronic renal insufficiency. In a recent review of 35 studies that had evaluated the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease, only four studies assessed the risk of cardiovascular events. In spite of the serious limitations observed in quality and methodology of the studies, the data showed a significant risk of cardiovascular mortality and cardiovascular events in relation to the disturbances in mineral metabolism among ESRD patients [16]. None of the studies independently assessed stroke or TIA. One of them assessed a composite outcome: myocardial infarction, heart failure, TIA or stroke; higher calcium levels were associated with adverse cardiovascular events [17].

The factors predictive of stroke in the follow-up were higher age, diabetes, and the diagnosis of AF prior to commencing dialysis, or AF diagnosis in the follow-up. Prior stroke was present in 17% of our patients, a proportion similar to the general population [18] and in the dialysis population [2]. Although the diagnosis of previous stroke had been demonstrated to be predictive of a new stroke in patients on dialysis [19] and in the general population [18,20], this has not been seen in our study. The lower survival, with death from causes other than stroke in 7 of 30 patients who began dialysis with stroke in the first 90 days of substitutive treatment, could explain these findings.

Although the relationship between AF and ischaemic stroke in the general population is a well established clinical finding, the information available on AF in patients on dialysis is scarce. There is accord with respect to the high prevalence of AF in dialysis patients [5], but there is no agreement regarding its thrombogenic capacity. Data from the ATRIA study showed that renal disease increases the risk of thromboembolism independently of other risk factors, and with a direct relationship between the grade of deterioration of renal function and the rate of thromboembolism [21]. In the earlier studies conducted in our institution, AF was a very frequent arrhythmia in dialysis, not only in prevalent patients [22,23] but also in incident patients [24]. In all of these patients, AF is a factor associated with a higher rate of thromboembolism [22–25]. However, other studies have not observed an increase in risk of stroke associated with AF [26,27]. In the recent CHOICE study of the incidence of stroke in patients on dialysis, the presence/absence of AF had not been investigated [3].

In the present study, almost a quarter of the patients who commenced dialysis having had a previous ischaemic stroke were diagnosed as having AF, and 20 of the 34 patients who had a stroke in follow-up had had AF before commencing dialysis or had developed it in follow-up. AF is an independent risk factor for ischaemic...
stroke in the clinical evolution of patients on dialysis. We believe that these findings carry new clinical information of importance, i.e. the relationship between ischaemic stroke and AF in the dialysis population is invaluable in establishing indications for anti-thrombotic treatment in this population; albeit, the risk associated with this therapy in the dialysis population has not as yet been sufficiently clarified [28–33]. In the absence of studies of anticoagulation in patients with AF on dialysis, our clinical approach, based on our current study and the results of our previous studies [22–25,28,29], is to prescribe oral anticoagulants to patients with AF according to the same criteria applied to the general population, i.e. for those without haemorrhagic risk and with cardioembolic risk factors associated with arrhythmia, according to the CHADS2 score [34].

Ischaemic ictus presented early in the present study. Eleven (32.3%) of the patients with stroke in follow-up had had the event within the first year on dialysis, with death resulting in six of these patients. Also, 6 of these 11 patients had been diagnosed with AF. This high mortality has been well documented in the dialysis population [8] and in the general population [18,35]. The principal cause of death evident in both populations was cardiovascular disease [8,35].

In summary, not only is the prevalence of ischaemic stroke elevated in the patient population on entry into the dialysis programme but so is the incidence of stroke during clinical follow-up, as well. The incidence of ischaemic stroke is 8-fold greater than that in the general population. The incidence of stroke is also greater in patients diagnosed as having AF in any of its forms, compared to those in sinus rhythm. The results of the present study confirm our previous findings which had demonstrated that this arrhythmia in patients on dialysis is an important risk factor in the presentation of ischaemic stroke, and as such, an anticoagulant treatment needs to be considered, following a risk–benefit evaluation of each patient.

Conflict of interest statement. None declared.

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Association of polymorphisms in the klotho gene with severity of non-diabetic ESRD in African Americans

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Abstract

Background. Non-diabetic forms of nephropathy commonly lead to end-stage renal disease (non-DM ESRD). Previous studies have demonstrated that African Americans are more susceptible to non-DM ESRD compared to other ethnic groups, and this risk has a strong genetic component. A genome-wide scan for ESRD in African American families enriched for non-DM ESRD showed evidence for linkage in chromosome 13q33,3, and a candidate gene in this region, klotho, was selected for a detailed analysis in a follow-up case-control association study.

Methods. Thirty-four single-nucleotide polymorphisms (SNPs) in the klotho gene were genotyped in 317 unrelated African American non-DM ESRD cases and 354 non-nephropathy controls, including 12 SNPs identified by re-sequencing a region around exon 4.

Results. Two SNPs demonstrated modest admixture-adjusted evidence of association with non-DM ESRD, rs650439 (P = 0.013, recessive model) and rs643780 (P = 0.017, recessive model), while rs17643698 approached significance (P = 0.0953, two degrees of freedom test). Eight of the most significant SNPs were tested for replication in a second case-control collection (557 African American non-DM ESRD cases and 187 controls), and there was no evidence of association in replicate cases and controls; nor when the samples were combined for a total of 874 non-DM cases and 541 controls. Cox proportional hazards models were computed to test for association between polymorphisms in klotho and age at onset of ESRD. A three-SNP haplotype, rs526906, rs525014 and rs526908 (T/T/T), was associated with age of onset of ESRD [P = 0.007, recessive model; hazard ratio (HR) = 0.70]. Subjects homozygous for this haplotype had a mean 4 years later onset of ESRD, suggesting a slower disease progression. HapMap subjects homozygous for this haplotype had increased expression of klotho, further supporting a protective role of this variant in ESRD.

Conclusion. We conclude that three SNPs in intron 1 of the klotho gene are associated with delayed age at onset of non-DM ESRD in African Americans.

Keywords: genetics; klotho; non-diabetic ESRD

Introduction

Non-diabetic forms of end-stage renal disease (non-DM ESRD), typically coded as hypertension-associated and secondary to chronic glomerular diseases, contribute to >40% of ESRD in African Americans. African Americans are particularly vulnerable to non-DM ESRD, having a 4-fold increased risk compared to European Americans. We [1] reported previously that African Americans are nine times more likely to develop ESRD if they have...

[References and further details are omitted for brevity.]